

RESEARCH ARTICLE

A Lymph Node Staging System for Gastric Cancer: A Hybrid Type Based on Topographic and Numeric Systems

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Abstract

Although changing a lymph node staging system from an anatomically based system to a numerically based system in gastric cancer offers better prognostic performance, several problems can arise: it does not offer information on the anatomical extent of disease and cannot represent the extent of lymph node dissection. The purpose of this study was to discover an alternative lymph node staging system for gastric cancer. Data from 6025 patients who underwent gastrectomy for primary gastric cancer between January 2000 and December 2010 were reviewed. The lymph node groups were reclassified into lesser-curvature, greater-curvature, and extra-perigastric groups. Presence of any metastatic lymph node in one group was considered positive. Lymph node groups were further stratified into four (new N0–new N3) according to the number of positive lymph node groups. Survival outcomes with this new N staging were compared with those of the current TNM system. For validation, two centers in Japan (large center, $n = 3443$; medium center, $n = 560$) were invited. Even among the same pN stages, the more advanced new N stage showed worse prognosis, indicating that the anatomical extent of metastatic lymph nodes is important. The prognostic performance of the new staging system was as good as that of the current TNM system for overall advanced gastric cancer as well as lymph node—positive gastric cancer (Harrell C-index was 0.799, 0.726, and 0.703 in current TNM and 0.799, 0.727, and 0.703 in new TNM stage). Validation sets supported these outcomes. The new N staging system demonstrated prognostic performance equal to that of the current TNM system and could thus be used as an alternative.

Introduction

In the field of gastric cancer, the fifth most common cancer and a major leading cause of cancer-related deaths worldwide [1] and particularly in East Asia [2,3], the application of appropriate staging systems has been a widely discussed issue in both Eastern and Western countries. The current staging system for gastric cancer is based on the extent of the primary tumor, the extent of lymph node (LN) metastasis, and the presence of distant metastases [4]. Although the staging for the extent of the primary tumor (T stage) is based on the depth of tumor invasion into the gastric wall, the staging for the extent of LN metastasis (N stage) has been converted from an anatomical location—based system to a numeric-based system [5,6]. Moreover, within this numeric-based system, the cutoff value of number of metastatic LNs defining the pN category has been changed. The purpose of this conversion was to predict prognosis more accurately [7–9] and to more easily perform comparisons with previous anatomical-based classifications [10]. However, the numeric-based N staging system has limitations, including its lack of information on the anatomical extent of the disease and its discordance between preoperative and postoperative N staging [11], as there is no way to determine the number of metastatic LNs prior to an operation; furthermore, the system cannot represent the extent of LN dissection despite the use of radical LN dissection (D2) as standard treatment [6,12,13].

The stomach is an organ to which blood is supplied by five main vessels (right and left gastropiploic arteries, right and left gastric arteries, and short gastric artery); thus, it has an abundant and complicated lymphatic network system [14]. This complexity of the lymphatic network system for gastric cancer hinders the use of an anatomical-based system. However, the anatomical location of metastatic LNs is nevertheless important, as their locations depend on the location and severity of the primary cancer in the stomach; thus, it must be considered when staging gastric cancer. Therefore, an alternative N staging system that can simply and specifically represent the anatomic extent of the disease and provide accurate prognosis must be developed. To this end, we reclassified the LNs near the stomach and proposed a new staging system for gastric cancer based on a new N category.

Methods

Study design and participants

The data from patients who underwent gastrectomy for primary gastric cancer at Yonsei University Hospital between January 2000 and December 2010 were reviewed. The Institutional Review Board of Yonsei University Hospital agreed to exempt written informed consent from the participants and approved this study (4-2012-0798). To validate the new staging system, two hospitals in Japan were invited to participate in this study: one was the largest cancer center in Japan, National Cancer Center (NCC) Hospital (January 2000 to December 2007), and the other was a medium volume center, Tokyo University Hospital (TU; January 2004 to December 2010).

Inclusion and exclusion criteria

All patients were pathologically confirmed to have primary gastric cancer. Minimally invasive surgery, such as laparoscopic or robotic gastrectomy, was excluded, and patients with any distant metastases (including peritoneal seeding and para-aortic LN metastasis) were excluded. Additional exclusion criteria were as follows: 1) cases in which the locations of LNs were not divided, 2) patients who underwent preoperative chemotherapy, and 3) patients with metastatic LNs of unclear locations. Ultimately, a total of 6025 patients were enrolled in this study.

and analyzed. In the validation sets, the criteria were identical for the NCC set ($n = 3443$), and minimally invasive surgery was additionally included in the TU set ($n = 560$).

The extent of LN dissection and postoperative treatment

The surgical extent of LN dissection was based on the Japanese Classification of Gastric Carcinoma [10]. The operator divided the location of each LN just after the operation, according to the Japanese classification [6,10,15], and the pathologist reviewed and reported the status of each LN. Adjuvant therapy was administered when a patient was diagnosed with at least stage II gastric cancer, and the standard strategy of chemotherapy involved a 5-fluorouracil based regimen.

Classification of LN groups based on anatomical locations

LN groups could be divided roughly into perigastric LN groups and extra-perigastric (EP) LN groups. Given the anatomical characteristics of the stomach, with lesser curvature (LC) and greater curvature (GC) sides, we divided perigastric LNs into two groups: LC (1, 3, 5) and GC (2, 4sa, 4sb, 4d, 6, and greater omentum). The remaining LNs, which were located in EP area (except the para-aortic area) were classified as the EP group (Fig 1). Regardless of the number of metastatic LNs, if any metastatic LN was involved in one group, we considered the corresponding group to be positive for metastasis. Finally, we stratified the status of LN groups into four categories: 1) new N0, indicated by no metastatic LN in any group; 2) new N1, indicated by one positive LN among three groups (positive LC alone, positive GC alone, or positive EP alone), regardless of number; 3) new N2, indicated by two positives out of three groups (positive LC + GC, positive LC + EP, or positive GC + EP), regardless of number; and 4) new N3, defined as positive results for all three groups (LC + GC + EP).

A proposed new classification for the N staging system

To determine whether this new N classification could act as an N staging system, we compared prognostic performances with those of the current pN staging system, the 7th edition of tumor-node-metastasis (TNM) from UICC [16]. The new N classification was combined with the current pT staging system, and a new TNM staging system was established. The new staging system was compared with the results of the current TNM system, including substages.

Statistical analysis

A Kaplan-Meier analysis was performed to evaluate overall survival (OS). Survival data was represented as patient mean survival as it was not always possible to calculate median survival. The log-rank test and Cox proportional hazards model were used to compare the OS of the new staging system and the current TNM staging system. Kappa values were applied to evaluate the degree of conformity between the two staging systems. To compare the prognostic performance of each staging system, the Harrell C-index [17] (measuring the predictive accuracy of survival outcome) was used. A C-index of 1.0 indicated 100% predictive accuracy. In all cases, a p -value of less than 0.05 was considered to be statistically significant. The statistical analyses were performed using IBM SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) and R software version 2.15.2 with the “survival” package.

Results

Patient demographics

The mean age of enrolled patients was 57.6 ± 11.8 years, and 33.6% were female (Table 1). Of 6025 patients, 1387 (23.0%) underwent total gastrectomy, and the mean number of retrieved

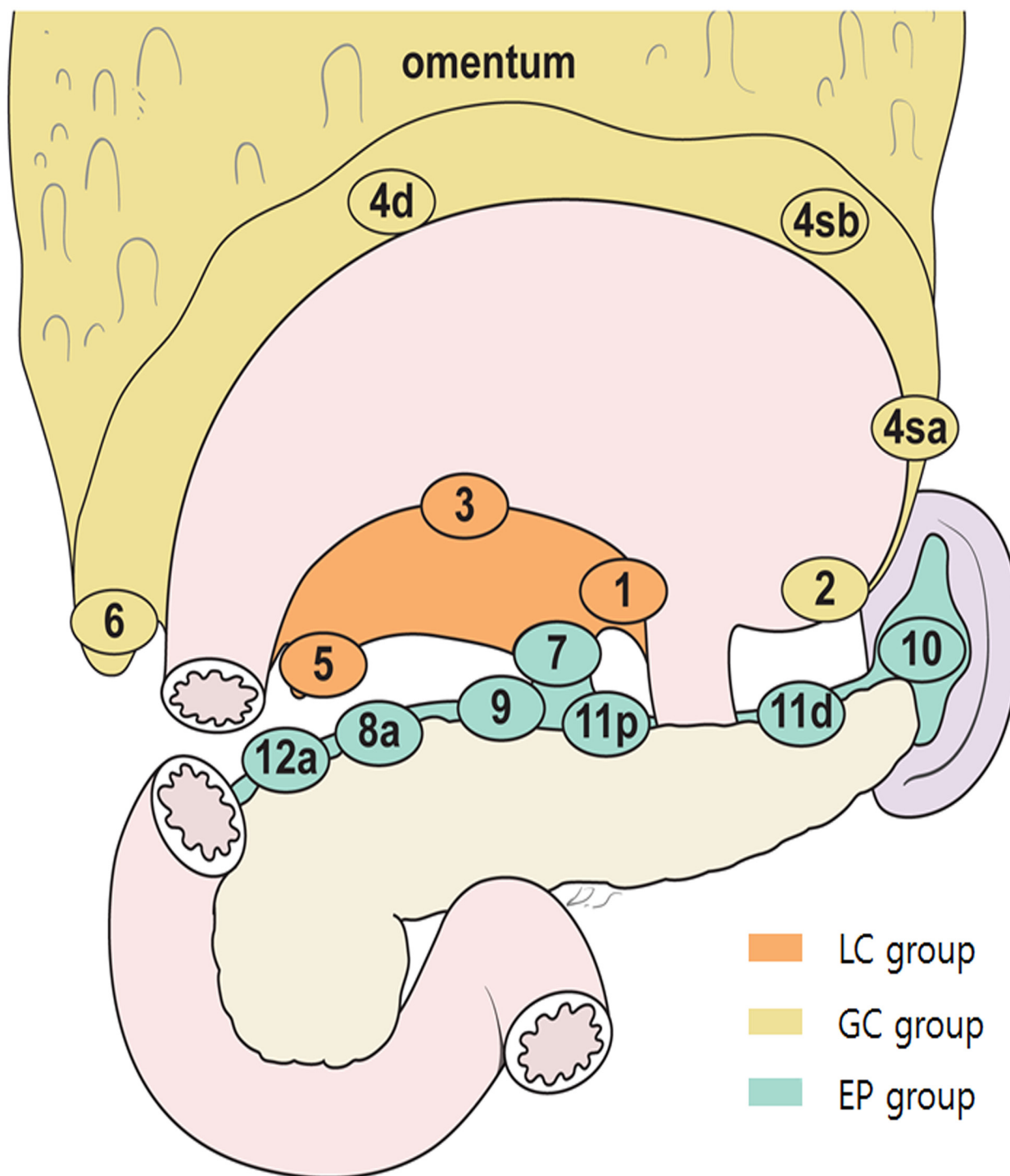


Fig 1. Classification of lymph node groups based on anatomical location. Lesser curvature (LC) group (station number 1, 3, and 5, according to Japanese classification), greater curvature (GC) group (station number 2, 4sa, 4sb, 4d, 6), and extra-perigastric (EP) group.

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LN was 40.7 ± 15.5 . The distribution of pT stage was similar to recently published reports [18–20]. The mean number of metastatic LNs was 3.2 ± 7.4 (8.5 ± 10.1 in lymph node—positive patients), and the median follow-up was 60 months.

Table 1. Patient demographics and characteristics of gastric cancer.

Variables	Yonsei (n = 6025)	NCC (n = 3443)	TU (n = 560)
Age (years), mean \pm SD	57.6 \pm 11.8	62.0 \pm 11.6	65.6 \pm 11.6
Sex			
Male, n (%)	4002 (66.4%)	2346 (68.1%)	395 (70.5%)
Female, n (%)	2023 (33.6%)	1097 (31.9%)	165 (29.5%)
Extent of gastrectomy			
Distal, n (%)	4633 (76.9%)	1649 (47.9%)	230 (41.1%)
Total, n (%)	1387 (23.0%)	809 (23.5%)	137 (24.4%)
[†] Others, n (%)	5 (0.1%)	985 (28.6%)	193 (34.5%)
pT stage			
mucosa, n (%)	1641 (27.2%)	946(27.5%)	123 (22%)
submucosa, n (%)	1369 (22.7%)	1169(34.0%)	207 (37.0%)
proper muscle, n (%)	780 (12.9%)	378(11.0%)	59 (10.5%)
subserosa, n (%)	665 (11.0%)	455(13.2%)	92 (16.4%)
serosa, n (%)	1506 (25.0%)	464(13.4%)	75 (13.4%)
adjacent organ, n (%)	64 (1.1%)	31(0.9%)	3 (0.5%)
Number of metastatic LNs			
Mean \pm SD	3.2 \pm 7.4 (8.5 \pm 10.1)*	1.7 \pm 4.1(5.2 \pm 5.9)*	2.2 \pm 6.1 (7.0 \pm 9.3)*
0, n (%)	3794 (63.0%)	2326(67.6%)	386 (68.9%)
1–2, n (%)	716 (11.9%)	488(14.2%)	64 (11.4%)
3–6, n (%)	600 (10.0%)	335(9.7%)	51 (9.1%)
7–15, n (%)	541 (9.0%)	219(6.4%)	42 (7.5%)
\geq 16, n (%)	374 (6.2%)	75(2.2%)	17 (3.0%)
Retrieved LNs, mean \pm SD	40.7 \pm 15.5	43.0 \pm 72.9	38.4 \pm 20.1

LN, lymph node; SD, standard deviation; NCC, National Cancer Center Hospital in Japan; TU, Tokyo University Hospital in Japan

*mean and SD of the number of metastatic LNs except pN0

[†] pylorus-preserving gastrectomy or proximal gastrectomy

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In validation sets, baseline characteristics were similar to the original set, except for the extent of gastrectomy: pylorus-preserving or proximal gastrectomy cases were more frequently performed in Japan. The median follow-up period was 77 months in the NCC set and 48 months in the TU set.

Characteristics of the new N classification

If the metastatic LN numbers were limited to only those near the perigastric area, the mean number of metastatic LNs was 3.6 ± 3.6 , and if this area was expanded to the EP area, the mean number was 13.7 ± 11.9 (Table 2). The mean numbers of metastatic LNs according to the new N classification were 2.2 ± 1.9 , 6.7 ± 5.2 , and 17.5 ± 12.2 in the new N1, new N2, and new N3 groups, respectively. The Kaplan-Meier curves of OS for each combination of the status-based LN groups showed that the new classification provided a well-stratified prognosis for gastric cancer (Fig 2A).

Comparison of survival among new N stages for each pN stage

The differences in patient survival among the new N stages according to pN stage (according to 7th edition of the TNM [16]) are presented in Fig 2B, 2C, and 2D. When the numbers of metastatic LNs were one or two (pN1), the new N2 group had a poorer prognosis than the new N1

Table 2. Number of metastatic lymph nodes for each combination of the three status-based groups.

	Number of patients (%)	Mean metastatic LNs \pm SD
Perigastric LN metastasis	1137 (18.9%)	3.6 \pm 3.6
Extra-perigastric LN metastasis	1094 (18.1%)	13.7 \pm 11.9
new N0	3794 (63.0%)	0
new N1	898 (14.9%)	2.2 \pm 1.9
LC alone	407 (6.8%)	2.2 \pm 1.8
GC alone	385 (6.4%)	2.3 \pm 2.0
EP alone	106 (1.8%)	2.1 \pm 1.8
new N2	583 (9.7%)	6.7 \pm 5.2
LC + GC	345 (5.7%)	6.5 \pm 4.8
LC + EP	124 (2.1%)	6.5 \pm 4.8
GC + EP	114 (1.9%)	7.5 \pm 6.4
new N3	750 (12.4%)	17.5 \pm 12.2
LC + GC + EP	750 (12.4%)	17.5 \pm 12.2

LN, lymph node; SD, standard deviation; LC, lesser-curvature group; GC, greater-curvature group; EP, extra-perigastric group;

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group (Fig 2b) with statistical significance ($p < 0.001$). When the number of metastatic LNs was between 3 and 6 (pN2), there was no significant difference between the new N1 and new N2 groups; however, the prognosis of the new N3 group was worse than the new N2 group and the new N1 group (Fig 2c; $p = 0.045$ and 0.011 , respectively). For pN3 (metastatic LNs ≥ 7), the prognosis of the new N3 group was worse than the new N1 and new N2 groups (Fig 2d; $p < 0.001$ for both).

Relationship between the new staging system and the TNM 7th edition system

The patient distributions of the new N classification and the pN staging system of the TNM 7th edition are shown in Table 3. The kappa value between the pN stage of the TNM 7th edition and new N classification systems was 0.803. In comparing the distributions of the new TNM staging system (combined pT stage of TNM 7th edition with new N classification) and TNM 7th edition system, the kappa value was found to be 0.856. The number of patients in each stage was well-distributed in both staging systems.

Comparison of prognostic performance between the new staging system and the TNM 7th edition system

The hazard ratios (HRs) for pN1, pN2, and pN3, compared to pN0, were 2.5, 3.8, and 11.0, respectively, in the current TNM 7th edition. In the new N classification, the HRs of new N1, N2, and N3, compared to new N0, were 2.6, 5.3, and 11.2, respectively, which indicates that the new N stage system shows a similar distribution to the current N staging system (Table 4).

The HRs of each TNM substage (Ib, IIa, IIb, IIIa, IIIb, and IIIc), which were compared to Ia, were 2.1, 2.3, 4.5, 5.5, 9.3, and 19.3 in the current TNM 7th edition system and 1.9, 2.9, 4.1, 6.4, 11.0, and 20.2 in the new TNM staging system, respectively. In the validation sets, the distributions of the HRs of each substage were similar between the new TNM stage and the TNM 7th edition.

According to the Kaplan-Meier curves, prognoses were well-stratified for each substage, not only in the original set but also in the validation sets (Fig 3A to 3F). Harrell's C-index, which

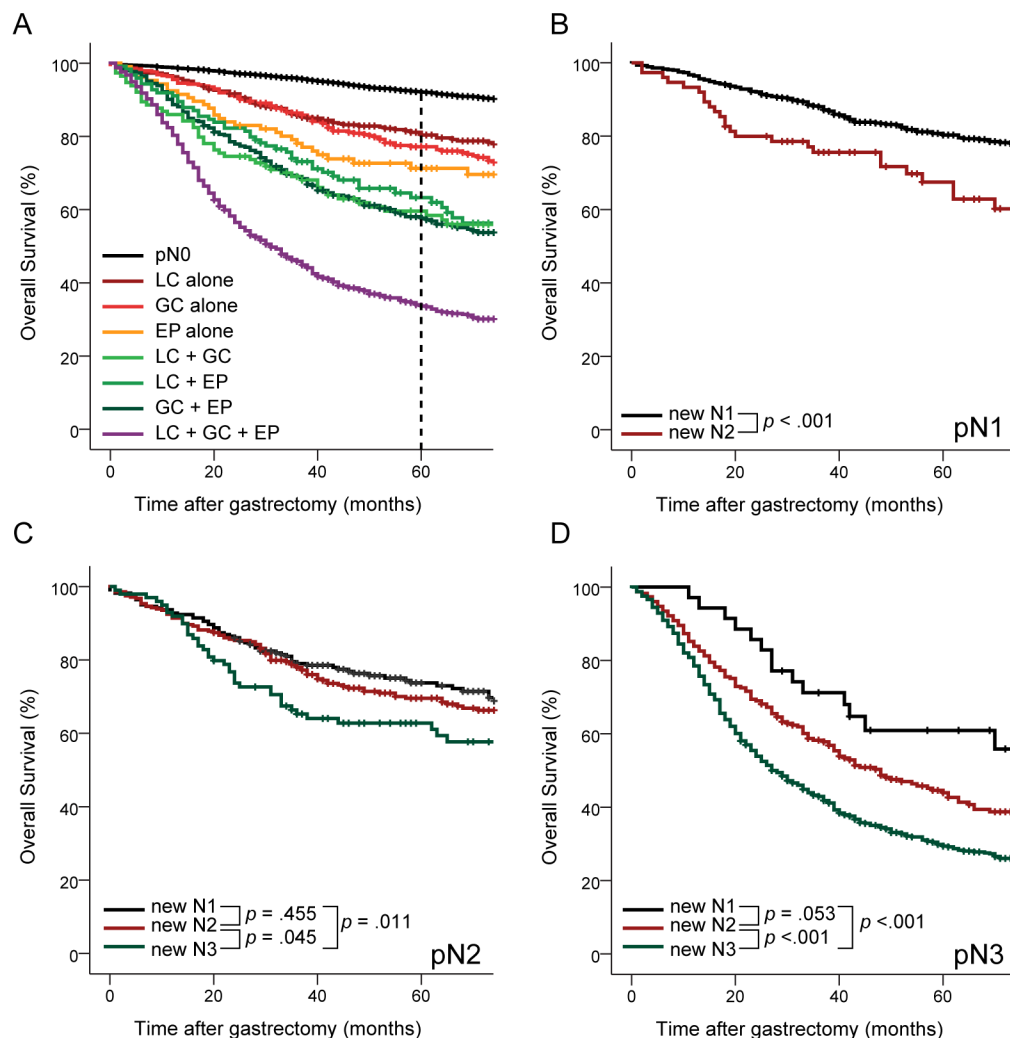


Fig 2. Overall survival for new N stages. A) patient survival among each combination of status-based lymph node groups, B) patient survival for each new N stage at pN1 (number of metastatic lymph nodes: 1–2), C) patient survival for each new N stage at pN2 (number of metastatic lymph nodes: 3–6), D) patient survival for each new N stage at pN3 (number of metastatic lymph nodes: ≥ 7). LC, lesser-curvature group; GC, greater-curvature group; EP; extra-perigastric group.

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indicates prognostic performance, was 0.799 (95% CI: 0.792–0.806) and 0.799 (95% CI: 0.792–0.806) in the TNM 7th edition and new TNM staging systems, respectively, and there was no significant difference between the two ($p > 0.999$; Table 5). In addition, the C-index of the new TNM staging system was comparable to that of the TNM 7th edition for advanced GC and LN-positive GC (0.726 and 0.703 for TNM 7th edition vs. 0.727 and 0.703 for new TNM staging system; $p = 0.937$ and 0.999 , respectively). The results from NCC and TU validated the prognostic performance of the new TNM staging system and were nearly identical to the current TNM 7th edition system.

Discussion

The present results suggest that the more advanced new N stages were indicative of a worse prognosis, even for the same current pN stage, implying that the anatomical extent of lymph node metastasis is an important factor for gastric cancer prognosis and needs to be applied to

Table 3. Patient distributions for the TNM 7th edition and new staging system.

		TNM 7 th edition							
		pN0	pN1	pN2	pN3	total			
	new N0	3794	0	0	0	3794			
	new N1	0	641	222	35	898			
	new N2	0	75	279	229	583			
	new N3	0	0	99	651	750			
	total	3794	716	600	915	6025			
New staging system		Ia	Ib	IIa	IIb	IIIa	IIIb	IIIc	total
	new Ia	2721	0	0	0	0	0	0	2721
	new Ib	0	641	31	0	0	0	0	672
	new IIa	0	23	433	54	6	0	0	516
	new IIb	0	0	19	513	74	13	0	619
	new IIIa	0	0	0	29	289	136	15	469
	new IIIb	0	0	0	0	42	237	144	423
	new IIIc	0	0	0	0	0	59	546	605
	total	2721	664	483	596	411	445	705	6025

kappa value = 0.803 (between new N stage and pN 7th stage), 0.856 (between new TNM stage and TNM 7th stage)

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gastric cancer staging systems. Accordingly, this new staging system, which reflects the anatomical extent of lymph node metastasis, showed prognostic performance equal to that of the current TNM staging system; moreover, these findings were validated by data from other centers in Japan, supporting this newly proposed staging system as a good alternative to the current TNM staging system.

The most attractive point of our new staging system is its simplicity. With the new staging system, the N stage depends only on the presence of metastatic LNs in each group (LC, GC, and EP), regardless of the number of metastatic LNs. Counting the numbers of both retrieved and metastatic LNs is affected by pathologists or pathology technicians who discover and manipulate LNs in the resected specimens [21], which is one factor related to stage migration. Although this problem can also affect the new staging system, we expect that this new system could reduce any variations or errors in reporting and decrease stage migration, as counting all of the LNs is not necessary. For example, if there is lymph node metastasis in each of the three groups (LC, GC, and EP), it would be sufficient to access only three lymph nodes, one from each group, rather than performing a whole lymphadenectomy. Furthermore, the new staging system unifies preoperative and postoperative staging reports in gastric cancer. As it is difficult to measure the presence and number of metastatic LNs preoperatively with current radiologic tools [4,22,23], an anatomical-based staging system would be more appropriate than a numeric N staging system, which requires counting all suspicious metastatic LNs preoperatively. Additionally, one suspicious metastatic LN in a preoperative image could in fact be more than one metastatic LN. Accordingly, our staging system is not influenced by the number of metastatic LNs and is only affected by the presence of a metastatic LN in at least one of three groups (LC, GC, or EP). Thus, we expect that our newly proposed staging system would make preoperative staging easier, particularly when there is an LN large enough to be detected, and this would also mean that histological results would be those of the preoperative staging.

Another advantage of the new staging system is that it can represent the extent of LN dissection. After a long debate about the advantages of D2 LN dissection [24–28], it is currently considered to be the standard operative procedure in Asian countries [6] and is also recommended

Table 4. Hazard ratios from Cox proportional hazard model and mean survival rates for the TNM 7th edition and the new staging system.

	TNM 7th			New staging system		
	HR	p-value	mean survival (months)	HR	p-value	mean survival (months)
N0	1	-	135.7 (133.3–138.1)	1	-	135.7 (133.3–138.1)
N1	2.5 (2.1–3.0)	< .001	109.9 (105.8–113.9)	2.6 (2.2–3.1)	< .001	111.7 (107.7–115.6)
N2	3.8 (3.2–4.4)	< .001	101.7 (95.4–107.9)	5.3 (4.6–6.2)	< .001	89.4 (83.6–95.2)
N3	11.0 (9.7–12.4)	< .001	55.4 (51.8–59.1)	11.2 (9.9–12.8)	< .001	54.5 (50.4–58.5)
Yonsei	1	-	143.3 (141.1–145.5)	1	-	143.3 (141.1–145.5)
Ia	1	-	143.3 (141.1–145.5)	1	-	143.3 (141.1–145.5)
Ib	2.1 (1.6–2.6)	< .001	128.1 (123.7–132.4)	1.9 (1.5–2.5)	< .001	129.2 (124.9–133.5)
IIa	2.3 (1.8–3.0)	< .001	120.7 (116.1–125.2)	2.9 (2.3–3.6)	< .001	116.4 (111.7–121.0)
IIb	4.5 (3.7–5.4)	< .001	107.6 (102.9–112.3)	4.1 (3.4–5.1)	< .001	109.9 (105.4–114.4)
IIIa	5.5 (4.5–6.8)	< .001	98.4 (92.8–104.1)	6.4 (5.3–7.8)	< .001	95.0 (89.2–100.7)
IIIb	9.3 (7.7–11.2)	< .001	82.3 (75.6–88.9)	11.0 (9.1–13.2)	< .001	76.2 (69.7–82.7)
IIIc	19.3 (16.5–22.7)	< .001	49.3 (45.4–53.2)	20.2 (17.1–23.8)	< .001	47.6 (43.5–51.7)
Ia	1	-	148.6(145.1–152.2)	1	-	148.6(145.1–152.2)
Ib	1.4(0.9–1.9)	0.096	147.1(143.5–151.6)	1.3(0.9–1.9)	0.112	148.1(144.0–152.1)
IIa	2.4(1.7–3.2)	< .001	137.9(132.3–143.4)	2.4(1.8–3.3)	< .001	136.3(130.5–142.2)
NCC	1	-	129.5(123.3–135.8)	1	-	128.6(122.7–134.6)
IIb	3.1(2.3–4.1)	< .001	129.5(123.3–135.8)	3.2(2.4–4.3)	< .001	128.6(122.7–134.6)
IIIa	5.8(4.4–7.6)	< .001	112.0(103.1–120.8)	5.8(4.4–7.6)	< .001	111.7(103.0–120.3)
IIIb	7.6(5.7–10.0)	< .001	100.4(90.4–110.4)	10.2(7.9–13.3)	< .001	87.9(77.8–98.0)
IIIc	13.5(10.4–17.4)	< .001	73.0(63.1–83.0)	13.3(10.1–17.7)	< .001	73.5(61.7–85.3)
Ia	1	-	101.9 (98.6–105.2)	1	-	101.9 (98.6–105.2)
Ib	1.3 (0.5–3.8)	0.613	87.1 (79.7–94.4)	1.3 (0.5–3.8)	0.62	87.1 (79.7–94.4)
IIa	1.0 (0.3–2.8)	0.942	102.9 (96.3–109.6)	1.0 (0.3–2.8)	0.94	103.0 (96.5–109.6)
TU	1	-	97.5 (90.1–105.0)	1	-	92.6 (84.4–100.9)
IIb	1.2 (0.4–3.4)	0.778	97.5 (90.1–105.0)	2.0 (0.9–4.5)	0.088	92.6 (84.4–100.9)
IIIa	4.3 (1.8–10.1)	0.001	80.9 (67.1–94.7)	3.8 (1.6–8.9)	0.002	79.2 (66.4–92.0)
IIIb	5.4 (2.6–11.3)	< .001	70.7 (58.3–83.1)	5.2 (2.4–11.0)	< .001	72.1 (59.8–84.5)
IIIc	7.4 (3.7–14.8)	< .001	61.6 (47.7–75.5)	9.0 (4.3–19.1)	< .001	55.3 (38.5–72.0)

NCC, National Cancer Center Hospital in Japan; TU, Tokyo University Hospital in Japan

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in Western countries[12,13] for advanced gastric cancer. Nevertheless, the current numeric staging system does not represent the extent of LN dissection in gastric cancer surgery, as D2 LN dissection is based on an anatomical perspective. Although the current TNM system recommends that at least 16 LNs should be evaluated pathologically [29], this number of LNs does not guarantee a D2 LN dissection, as D1 LN dissection can occasionally be achieved for more than 16 LNs and vice versa. By applying the new staging system, the extent of LN dissection is automatically reflected in the staging system, as EP LN dissection should be performed when using the new N staging system.

The previous Japanese classification [10], which guided the anatomy-based treatment of gastric cancer, provided direct surgical guidance [4] and the anatomic extent of disease necessary to carefully assess gastric cancer [30]. In order to collect information on the anatomical extent of LN involvement, each LN station should be identified and labeled before histopathological assessment. This procedure is typically performed after operation, as the *en bloc* removal of lymph nodes is the most important oncological principle to be maintained during surgery. For this reason, the identification and classification of LN stations could be subjective to arbitrary criteria depending on individual surgeons or pathologists. Therefore, the precise information on LN status might be ambiguous, in particular for LN 7, 8a, 9, and 11p, and only

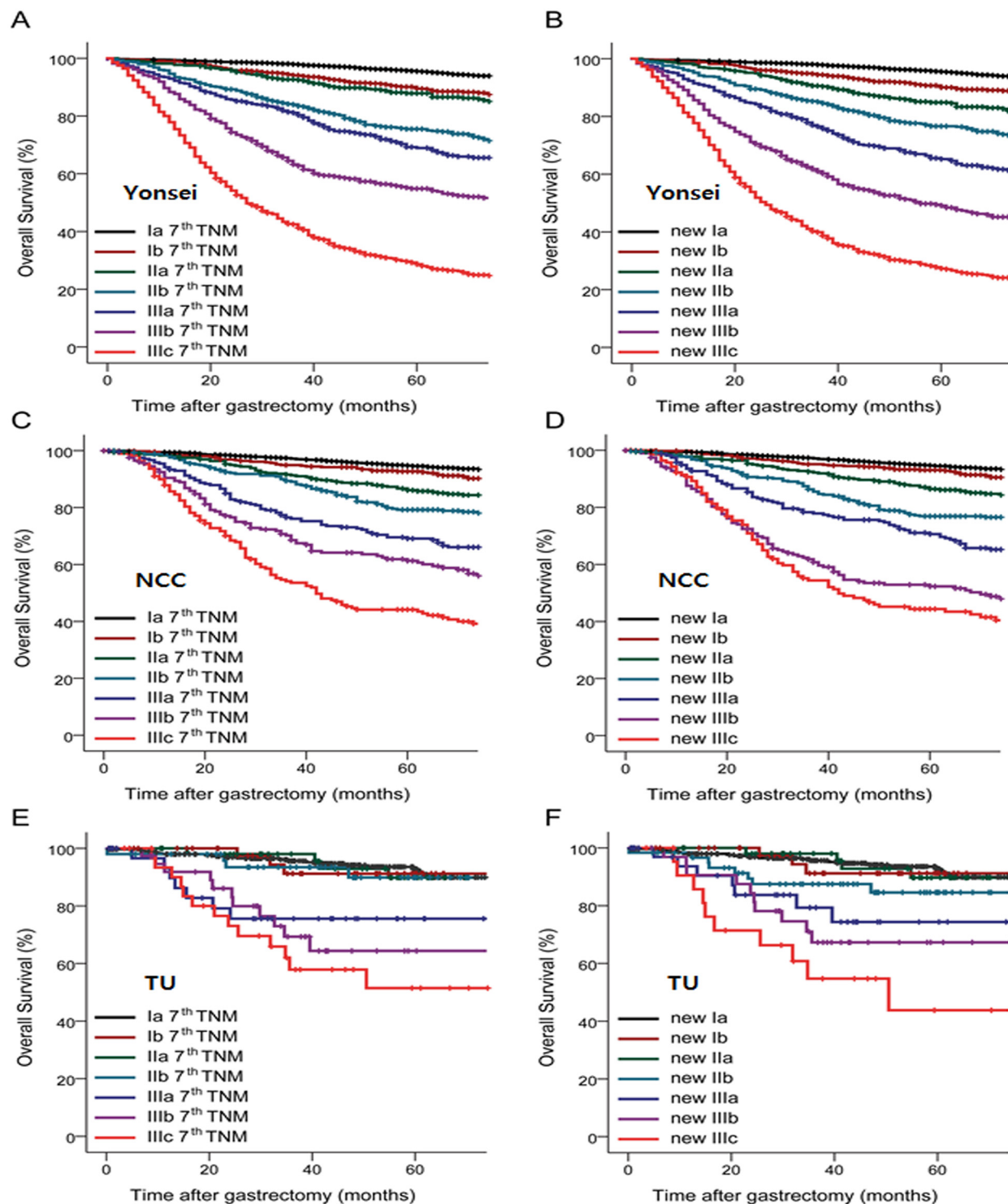


Fig 3. Kaplan-Meier curves for overall survival of each staging system. A) TNM 7th edition system with substages in Yonsei set, B) new TNM staging system with substages in Yonsei set, C) TNM 7th edition system with substages in NCC set, D) new TNM staging system with substages in NCC set, E) TNM 7th edition system with substages in TU set, F) new TNM staging system with substages in TU set. NCC, National Cancer Center in Japan; TU, Tokyo University Hospital in Japan.

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Table 5. The prognostic performance of each staging system (Harrell C-index) at each center.

	TNM	New TNM	p-value
Overall			
Yonsei	0.799(0.792–0.806)	0.799(0.792–0.806)	>.9999
NCC	0.747(0.736–0.758)	0.748(0.737–0.759)	0.9487
TU	0.703(0.669–0.737)	0.701(0.667–0.735)	0.9668
AGC			
Yonsei	0.726(0.717–0.735)	0.727(0.718–0.736)	0.9374
NCC	0.695(0.680–0.710)	0.700(0.685–0.715)	0.8137
TU	0.702(0.656–0.748)	0.698(0.652–0.744)	0.9510
LN positive			
Yonsei	0.703(0.694–0.712)	0.703(0.694–0.712)	>.9999
NCC	0.696(0.680–0.712)	0.701(0.685–0.717)	0.8251
TU	0.688(0.639–0.737)	0.682(0.634–0.730)	0.9303

NCC, National Cancer Center Hospital in Japan; TU, Tokyo University Hospital in Japan

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imperfect information may be available despite an increased level of complexity. With this possible reason among others, the Japanese classification system now uses a numeric-based N staging system that is divided into classification [15] and treatment guidelines [6]. Our new N classification is based on the modified anatomical location of metastatic LNs, which can represent the anatomical extent of the disease. This new system could decrease the variations among surgeons or pathologists while providing essential information on the extent of LN metastasis by identifying the location of each LN group, as LC, GC, and EP classifications are unambiguous. Consequently, it would facilitate accurate communication across institutions worldwide regarding LN staging, as this novel concept is intuitive and easier to understand than the original Japanese classification.

The main limitation of this study was that the present findings were not validated in a Western population; rather, the outcomes were only from centers in East Asia. To generalize these results, validation from Western countries is essential, as not only the epidemiology and treatment strategies but also the biology of gastric cancer in Asian patients and Europeans are different [31–33]. Validation in a western population may give further insight into the potential value of the new N staging system and perhaps allow global consolidation of LN staging in gastric cancer.

Several alternative staging systems for estimating the extent of LN metastasis in gastric cancer have been proposed, such as the LN ratio [34–38] (number of metastatic LNs / number of retrieved LNs) and the Kiel classification [39], which attempts to reflect biological tumor properties. However, these proposed staging systems cannot actually solve the aforementioned problems with the current TNM system, as they use the same numeric-based N staging. Moreover, the LN ratio system was criticized for the arbitrarily determined cutoff points, and the Kiel classification failed to be validated by recent studies from the same country [40]. Our novel LN staging system is intuitive and simple, can provide improved communication across institutions worldwide, can be used in preoperative staging, and can represent the extent of LN dissection and the anatomical extent of the disease. Furthermore, our results demonstrate that it offers substantial prognostic performance with validation. This novel N staging system may be a useful alternative to current numeric-based staging systems for gastric cancer.

Conclusion

Our novel N classification system for gastric cancer, which is based on modified anatomical location, is simple, intuitive, reasonable, easy to apply in clinical practice, and could improve communication among gastric cancer teams and centers. Application of our system may resolve the inherent problems of current numeric N staging systems. Accordingly, we suggest that our staging system may be a good alternative for gastric cancer staging.

Supporting Information

S1 File. Patients' clinical dataset.
(XLSX)

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Author Contributions

Conceived and designed the experiments: YYC JYA SHN. Performed the experiments: YYC JYA TF YO DWK. Analyzed the data: YYC JYA DWK. Contributed reagents/materials/analysis tools: YYC JYA TF YO HK WJH JHC HIK YS. Wrote the paper: YYC JYA HK YS TF YO DWK HIK JHC WJH SHN.

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